Remarks

Claims 1-39 are currently pending and claims 1-26 stand rejected. By the foregoing amendment, claims 1-5, 8, 9, 15-18 and 22 have been amended, claims 27-39 have been cancelled, and new claim 40 has been added. No new matter is presented by way of this amendment.

Election Pursuant to Restriction Requirement

Pursuant to the Examiner's restriction requirement in the September 7, 2005 Office Action, Applicant hereby elects without traverse the invention of Group 1, claims 1-26, for prosecution in this case. Claims 27-39 are cancelled herein, withdrawn from consideration and reserved for filing in a future application.

Further, the Examiner has required that the Applicant elect a specific species, i.e. a specific drug. Applicant hereby elects the species of insulin.

Claims Objections

The Examiner has noted objections to certain informalities in the percentage by weight of the components as recited in claims 9 and 22. Claims 9 and 22 have been amended to clarify water's percentage by weight. Support for this amendment can be found in the specification at pages 8-9. No new matter is added by this amendment.

Claim Rejections – 35 U.S.C §112

The Examiner has rejected claims 4, 5, 17 and 18 as indefinite under 35 U.S.C. §112 as containing the tradenames E200 and E400 to designate the polyglycol used, specifically by indicating their molecular weight in an abbreviated fashion. Applicant has amended these claims to remove tradenames and provide correct language to specify

the polyglycol by molecular weight. Support for this amendment can be found in the specification at pages 6 and 7. No new matter is added by this amendment.

Claim Rejections – 35 U.S.C §102(b)

The Examiner has rejected claims 1-3, 6, 8, 14-16, 19 and 21 under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 6,214,375 to Modi. Applicant respectfully disagrees for the following reasons.

As amended herein, claims 1 and 15, including and all of their dependent claims 2-14 and 16-26, respectively, include the elements of a carrier composition for transdermal delivery of a macromolecule comprising a polyenylphosphatidylcholine-enriched phosphatidylcholine component (*see* Application at ¶[0013]) entrapping a macromolecule for delivery to dermal vasculature (*see id.* at ¶[0013]), and further, wherein the component stabilizes said macromolecule at room temperature. (*See id.* at ¶[0006], [0015],[0022], [0027].) Modi fails to disclose or suggest at least these claim elements, and hence does not anticipate or render obvious the present claims, as detailed below.

Modi discloses phosphatidylcholine formulations to be used for the oral, parenteral or topical delivery of pharmaceuticals (*see* Modi, Abstract) in order to improve drug delivery and distribution within the body. (*Id.,* col. 1, lines 27-30.) Modi's formulations disclose a combination of *at least three* phosphatidylcholine compounds, including, among other many disclosed possibilities, egg phosphatidylcholine (col. 2, line 22) and soy lecithin (col. 2, line 22), and at least two biodegradable polymers, including, among other disclosed possibilities, polyethylene glycol, particulary disclosed as having a molecular weight of 1000-100,000 (*col.* 4, line 20). Further, Modi discloses the importance of use of "substantially saturated phosphatidylcholines" for stabilizing its liposomes. (*Id* .at col. 2, lines 52-53; col. 3, line 66.)

With respect to lecithin or phosphatidylcholine ("PC"), it is generally known that the soybean, sunflower and rapeseed are the main sources of commercial lecithin, and also, eggs themselves naturally contain phosphatidylcholine. In fact, lecithin such as

the egg yolk or soy lecithin employed in Modi, inherently includes other phospholipids besides phosphatidylcholine. In commercial lecithin products, such as those as disclosed in Modi, phosphatidylcholine may be present in various concentrations with most of the commercial lecithin products containing about 20% phosphatidylcholine. Further, Modi specifically discloses the importance of using use of *saturated* phosphatidylcholine.

In contrast, the present claims as amended require the use of polyenylphosphatidylcholine-enriched phosphatidylcholine ("PPC-enriched phosphatidylcholine"). (*See* claims 1 and 15.) As disclosed in the Application, PPC-enriched phosphatidylcholine is phosphatidylcholine bearing two fatty acid substituents, wherein at least one is an ***unsaturated*** fatty acid with at least two double bonds. (*See* Application ¶[0013].) Hence, the present claims require polyunsaturated phosphatidylcholine, specifically PPC-enriched phosphatidylcholine. In certain embodiments, pure PPC is employed (*see* claims 3 and 40*)* eliminating other phospholipids that may compete for absorption. (*See* Application ¶[0013].) Modi teaches use of phosphatidylcholine, and preferably those which are saturated. Hence, Modi not only fails to disclose or suggest, but further teaches away from use of PPC-enriched phosphatidylcholine which includes unsaturated fatty acids.

While PPC may ultimately be soybean-derived, the disclosure of egg or soy lecithin such as in Modi, does not inherently teach, nor does it suggest, the use of PPC-enriched PC, nor pure PPC. Hence, Modi's disclosure of lecithin, including soy lecithin, it does not teach or suggest use of PPC-enriched phosphatidylcholine as is required by the present claims, nor pure PPC (claims 3 and 40). For at least this reason, the present claims are patentable over Modi.

Further, Modi fails to teach or suggest the transdermal delivery of a macromolecule, such as insulin, to the dermal vasculature to enter the bloodstream, and hence, act internally in the body (and not merely upon the skin). As recited by the present claims, the present invention achieves transdermal delivery to replace oral or injected delivery of large molecule drugs (see Application ¶ [0010]) and instead,

achieves such delivery of large molecule drugs *through* the skin and into the vasculature to act internally upon the body. (*See* Application ¶[0014].) In contrast, Modi discloses use of liposome formulated drugs to stabilize drugs and but does not alter their traditional delivery route, i.e. oral, parenteral, topical. Modi discloses liposome formulated insulin *injections* (*see* Modi col. 1, lines 55-62) to increase therapeutic effect of these insulin treatments, but not to alter delivery means from injection to transdermal routes. (*See* Modi col. 1, line 63 to col. 2 line 7.) Modi does not achieve transdermal formulations that can carry large molecule drugs through the skin transdermally to the dermal vasculature. Any disclosure as to topical formulations in Modi relates solely to traditional small molecule delivery to the skin, to act upon the skin (versus transdermal delivery *through* the skin to enter the dermal vasculature, i.e. and the blood stream, and act internally). Hence, Modi does not teach or suggest formulations that transdermally deliver macromolecules to the vasculature as is required by the present claims. For at least this reason, the present claims are patentable over Modi.

Finally, the present claims recite that the PPC-enriched component of the stabilizes the macromolecule at room temperature, overcoming a problem in the art of degradation of insulin formulations at room temperatures. (*Id.*at ¶[0006].) As discussed in the Application, this allows for ease transport and administration of insulin treatments. (*See id.* at ¶¶[0015],[0022], [0027].) Modi is void of any disclosure as to formulations that achieve stabilization of large molecule drugs, such as insulin, at room temperatures. Hence, Modi does not teach or suggest formulations that stabilize macromolecules at room temperatures as is required by the present claims. For at least this reason, the present claims are patentable over Modi.

Rejections under 35 U.S.C §103(a)

The Examiner has rejected claims 4, 5, 7, 9,17,18, 20 and 22 under 35 U.S.C §103(a) as being unpatentable over U.S. Patent No. 4,687,661 to Kikucki et al. in view of U.S. Patent No. 6,294,192 to Patel et al.

As amended herein, claims 4, 5, 7, 9,17,18, 20 and 22 include the elements of a carrier composition for transdermal delivery of a macromolecule comprising a polyenylphosphatidylcholine-enriched phosphatidylcholine component (*see* Application at ¶[0013]) entrapping a macromolecule for delivery to dermal vasculature (*see id.* at ¶[0013]), and further, wherein the component stabilizes said macromolecule at room temperature. (*See id.* at ¶[0006], [0015],[0022], [0027].) Each of Kikuchi and Patel alone, or considered in combination, fails to disclose or suggest at least these claim elements, and hence does not render obvious the present claims, as detailed below.

Kikuchi discloses drug encapsulated liposome formulations directed towards industrial preparation of liposomes of uniform particle size. (Kikuchi col. 4, lines 9-11.) While Kikuchi generally discusses use of lecithin (just as Modi does), it is silent as to required element of polyenylphosphatidylcholine-enriched phosphatidylcholine. Kikuchi states there is no limitation on the drugs that can be encapsulated (col. 3, lines 55-56) and its mention of insulin within that list is not any more enabling for a large molecule drug such as insulin (and address the specific delivery problems associated therewith) than a typical small molecule drug. Hence, Modi does not teach or suggest to one of skill in the art the presently claimed carrier composition to achieve transdermal delivery of large molecules such as insulin, nor the ability to stabilize these compositions at room temperatures.

The Examiner cites Patel for disclosing use of polyethylene glycols in pharmaceutical compositions. In fact, Patel addresses delivery of *hydrophobic* therapeutic agents by enhancing their solubility in a carrier. (Patel Abstract.) As insulin is a macromolecule structured with two polypeptide chains linked by disulfide bonds, and *hydrophilic* in nature, one of skill in the art would not understand Patel as disclosing or suggesting compositions to carry insulin.

Further, any disclosure in Patel as to the use of polyethylene glycol for its surfactant properties (col. 6, lines 21-23), even if read in combination with Kikuchi, would not result in Applicant's carrier composition for transdermal delivery of a macromolecule which requires a polyenylphosphatidylcholine-enriched

phosphatidylcholine component entrapping a macromolecule for delivery to dermal vasculature, wherein the component stabilizes said macromolecule at room temperature. Patel, like Kikuchi, is silent as to each and every one of these aforementioned elements. Hence, Kikuchi in view of Patel does not render obvious the present claims, and the rejection has been traversed.

The Examiner has rejected claims 10, 11, 23 and 24 under 35 U.S.C §103(a) as being unpatentable over Modi in view of U.S. Patent No. 5,985,298 to Brieva et al. Applicant respectfully disagrees for the following reasons.

As discussed above, Modi fails to disclose or suggest at least the claim elements of a carrier composition for transdermal delivery of a macromolecule comprising a polyenylphosphatidylcholine-enriched phosphatidylcholine component entrapping a macromolecule for delivery to dermal vasculature, wherein the component stabilizes said macromolecule at room temperature. Brieva likewise fails to disclose these elements and remedy the defects in Modi.

Specifically, with respect to claims 10, 11, 23 and 24, the Examiner confirms that Modi is silent as to the addition of a surfactant and cites Brieva for disclosing use of non-volatile surfactants for improving adherence (of cosmetics) to the skin. (*See* September 7, 2005 Office Action at pp. 11-12.) In fact, Brieva discloses cosmetics having improved transfer resistance by use of the combination of trimethylated silica, volatile solvent and nonvolatile oil in conjunction (Brieva Abstract). While its disclosure mentions use of a silicone such as Dow 190 fluid (col. 3, line 63) as the nonvolatile component, its disclosure as to transfer resistance requires that this silicone be used in conjunction with the other named components (i.e. trimethylated silica and volatile solvent). Brieva contains no teaching or suggestion to incorporate one of its combined *cosmetic* ingredients to acheive adherence to skin and use it with Modi's pharmaceutical compostions that seek to improve drug distribution *within* the body. Further, even if Brieva's disclosure as to silicone fluids is read in combination with Modi, one of skill in the art would not arrive at Applicant's carrier composition for transdermal

delivery of a macromolecule which requires a polyenylphosphatidylcholine-enriched phosphatidylcholine component entrapping a macromolecule for delivery to dermal vasculature, wherein the component stabilizes said macromolecule at room temperature. Brieva, like Modi, is silent as to each and every one of these aforementioned elements. Hence, Modi In view of Brieva does not render obvious the present claims, and the rejection has been traversed.

The Examiner has rejected claims 12, 13, 25 and 26 under 35 U.S.C §103(a) as being unpatentable over Modi in view of U.S. Patent No. 6,538,061 to Chaiyawat et al. Applicant respectfully disagrees for the following reasons.

As discussed above, Modi fails to disclose or suggest at least the claim elements of a carrier composition for transdermal delivery of a macromolecule comprising a polyenylphosphatidylcholine-enriched phosphatidylcholine component entrapping a macromolecule for delivery to dermal vasculature, wherein the component stabilizes said macromolecule at room temperature. Chaiyawat likewise fails to disclose these elements and remedy the defects in Modi.

The Examiner has cited Chaiyawat, directed to cosmetic compositions, for its disclosure as to use of lubricating silicone fluids. Even if Chaiyawat's disclosure as to silicone fluids is read in combination with Modi, one of skill in the art would not arrive at Applicant's carrier composition for transdermal delivery of a macromolecule which requires a polyenylphosphatidylcholine-enriched phosphatidylcholine component entrapping a macromolecule for delivery to dermal vasculature, wherein the component stabilizes said macromolecule at room temperature. Chaiyawat, like Modi, is silent as to each and every one of these aforementioned elements. Hence, Modi In view of Chaiyawat does not render obvious the present claims, and the rejection has been traversed.

Double Patenting

The Examiner has entered a provisional rejection of claim 1-26 on the grounds of obviousness-type double patenting over claims 1-10 of co-pending Application No. 10/750,390. U.S. Patent Application No. 10/750,390 is directed to Methods for Formulating Stablized Insulin Compositions. In response to this rejection, a Terminal Disclaimer is submitted herewith, which should overcome the provisional double patenting rejection.

Conclusion

Applicant respectfully asserts that the Examiner's rejections have been traversed by the aforementioned amendment and remarks. It is respectfully submitted that all of the pending claims are in order for allowance and early notice to that effect is respectfully requested.

Respectfully submitted,

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Stephen P. McNamara, Registration No. 32,745
Helen M. Limoncelli, Registration No. 51,950
Attorneys for Applicants
ST.ONGE STEWARD JOHNSTON & REENS LLC
986 Bedford Street
Stamford, CT 06905-5619
203 324-6155